REMARKS

Rejection of Claims and Traversal Thereof

In the December 8, 2010 Office Action,

Claims 1-3 were rejected under 35 U.S.C.§102(e) as being anticipated by Soltero et al, (US Patent No. 6,770,625, hereinafter Soltero) as evidenced by Yamamoto et al., (US Patent No. 5,059,587, hereinafter Yamamota) ;

Claim 1was rejected under 35 U.S.C103(a) as being obvious over Lee et al (US Patent No. 6,506,730, hereinafter Lee);

Claim 1 was rejected under 35 U.S.C.§103(a) as being obvious over Russo (US Patent No. 5,976,788, hereinafter Russo) in view of Komarova et al. (*Calcif. Tissue Int.*73, 265-273 (published on line 6/6/2003), hereinafter Komarova) and Lee;

Claim 2 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and in view of Katre, et al (US Patent No. 4,917,888, hereinafter Katre '888) and Lee;

Claim 3 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and Katre, Crotts et al. (US 2003/0017203, hereinafter Crotts), Ekwuribe (US Patent No. 6,638,906, hereinafter Ekwuribe) and Lee; and

Claims 1-2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 15, 70 and 72 of US Patent No. 6,713,452.

Applicants traverse these rejections and insist that none of the cited references alone or in combination defeats the patentability of the presently claimed invention.

Rejection under 35 U.S.C.§102(e)

Claims 1-3 were rejected under 35 U.S.C.§102(e) as being anticipated by Soltero as evidenced by Yamamoto. Applicants insist that the Soltero reference, alone or in combination with Yamamoto does not disclose all the limitations of the presently claimed invention. Applicants have provided a specific amount by oral delivery for treatment of peripheral pain in a subject. The Soltera reference does not provide any guidance for an effective amount to treat peripheral pain in a subject of about 20 ug/kg at least once a day. Thus, this reference is not anticipatory and the rejection should be withdrawn.

Rejections under 35 U.S.C.§ 103(a)

1. Claim 1 was rejected under 35 U.S.C103(a) as being obvious over Lee. Applicants insist that Lee does not disclose, teach or suggest the presently claimed invention.

Applicants' invention, as set forth in claim 1, describes a method for **orally administrating** to the subject an effective amount of a **substantially monodispersed mixture of conjugates**, wherein the conjugate comprises a first oligomer and a second oligomer **conjugated at the Lys^{11} and Lys^{18} amine functionality of calcitonin and in an amount of about 20ug/kg at least once a day.**

According to the Office, Example 4 of the Lee reference shows the production of a diconjugate wherein pegylation occurs at Lys^{11} and Lys^{18} of calcitonin. Applicants submit that Example 4 does not teach a diconjugate with a PEG at both Lys^{11} and Lys^{18} functionality but instead Example 4 only teaches monconjugates. Example 4 refers to placement of PEG moieties at different pHs and this is discussed in the Brief Description of the Figures and shown in Figure 2, as recreated below.

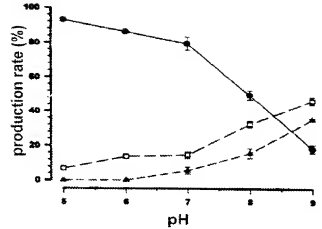
FIG. 2 shows the pH effect on the production of mono-PEG-sCT when PEG is conjugated with N-terminus of calcitonin, Lys^{18} or Lys^{11}, where

●: mono-PEG-sCT(N-terminal conjugate),

□: mono-PEG-sCT(Lys^{18}-conjugate),

▲: mono-PEG-sCT(Lys^{11}-conjugate).

FIG. 2



It is evident as stated in Example 4 that as the pH increases to 8 or above more monoconjugated calcitonin at the Lys^{11} and Lys^{18} amine functionalities is produced, albeit individually. There is nothing in this example that discusses, teaches or suggests a calcitonin conjugate with a PEG moiety at two lysine amine groups at the same time. Thus, this Lee reference does not teach or suggest each of the recited limitations of the presently claimed invention.

Further, the Lee reference only describes compositions for nasal administration and certainly never considers oral delivery in an amount of about 20ug/kg at least once a day.

Thus, the Lee reference does not teach or suggest the presently claimed invention, but instead teaches away from going in the direction of applicants' claimed invention. Specifically one skilled in the art reading Lee would quickly note that Lee is teaching away from any orally administered compounds.

The Office has stated numerous times that because injection causes pain that there is a need to develop other routes which is exactly what Lee accomplished. However, one reading this Lee reference would quickly note that Lee discourages the use of oral route, and as such, would never consider going in the oral direction just because an injection is painful. Lee immediately discussed the negative side effects

of oral administration and instead went in the direction of nasal delivery. For example, at the bottom of column 1, Lee discusses the disadvantages of oral compounds, as recreated below:

> In fact, the nasal mucosa is a direct absorption route through which drugs can circumvent the liver metabolism, which is a great hindrance to the utilization of drugs in the body upon oral administration. Thus, the nasal transmucosal route has an advantage over the oral route in that the body utilization of drugs can be significantly improved.

Further, Lee reiterates the negative side of oral administration at the bottom of column 3 and recreated below:

> As mentioned above, the nasal transmucosal delivery of peptides alone is significantly improved in absorption efficiency compared with the oral administration because the peptides are not subjected to liver metabolism, but poor in the bioavailability of the peptides because they are degraded by endogenous enzymes.

It is well settled in the law that if a cited reference teaches away from going in the direction of applicants' claimed invention then the Office has not established a *prima facie* case of obviousness. For example, Lee has expressly stated that orally administration of compositions is unacceptable because of the results that occur to the compound in the liver. According to the ruling in *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984), if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. This concept is further addressed in the MPEP, wherein section § 2143.01 V – VI states that:

> "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

Thus, even though the Office seems to be speculating that Lee does not discourage the use of oral route, the specification of Lee expressly states the direct opposite and does discourage a skilled artisan from

using an oral route. Thus, the Office has not established a *prima facie* case of obviousness and this rejection must be withdrawn.

2. Claim 1 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and Lee. Applicants insist that this proposed combination does not in any way teach and/or suggest the presently claimed invention.

The Office has already admitted that the Russo reference does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT. Further as stated, above, Lee does not teach or suggest PEGylation at Lys^{11} and Lys^{18} residues of CT and clearly teaches away from oral administration. Komarova teaches the use of PEGylated CT but only uses in vitro testing on HEK 293 cells. The reference muses about oral delivery but certainly never considers an oral delivery in an amount of about 20ug/kg at least once a day.

As the proposed combination does not teach or suggest each and every element of claim 1, applicants request the withdrawal of this rejection for obviousness.

3. Claim 2 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and in view of Katre and Lee. Applicants insist that the proposed combination suffers from the same shortcomings as that of the obviousness rejection of claim 1.

Russo does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT. Further as stated, above, Lee does not teach or suggest PEGylation at Lys^{11} and Lys^{18} residues of CT and clearly teaches away from oral administration. Komarova teaches the use of PEGylated CT but only uses in vitro testing on HEK 293 cells. The reference muses about oral delivery but certainly never considers an oral delivery in an amount of about 20ug/kg at least once a day. The addition of Katre does not overcome the shortcomings of the three references because even with all combined disclosures, the presently claimed invention is not disclosed, taught or suggested. As the proposed combination does not teach or suggest each and every element of claim 2, applicants request the withdrawal of this rejection for obviousness.

4. Claim 3 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova, Katre, Crotts, Ekwuribe and Lee. Applicants insist that the proposed combination suffers from the same shortcomings as that of the obviousness rejections of claims 1 and 2.

The Office has already admitted that the Russo reference does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT. Lee does not teach or suggest PEGylation at Lys^{11} and Lys^{18} residues of CT and clearly teaches away from oral administration. Komarova teaches the use of PEGylated CT but only uses in vitro testing on HEK 293 cells. The reference muses about oral delivery but certainly never considers an oral delivery in an amount of about 20ug/kg at least once a day. The addition of Katre or Crotts does not overcome the shortcomings of the Komarova, Russo and Lee references because the presently claimed invention is not disclosed, taught or suggested. As the proposed combination does not teach or suggest each and every element of claim 3, applicants request the withdrawal of this rejection for obviousness.

In light of the above discussion and the fact that each and every recited limitation of applicants' claimed invention is not disclosed or suggested in the cited references, applicants submit that the Office has not met its burden of establishing a *prima facie* case of obviousness. Accordingly, applicants respectfully request that all the above rejections of the pending claims, based on obviousness, be withdrawn.

Obviousness-Type Double Patenting

Claims 1-2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 15, 70 and 72 of US Patent No. 6,713,452. Applicants will file a Terminal Disclaimer when all other issues relating to patentability have been withdrawn.

Petition for Extension and Fees Payable

Applicants petition for a two (2) month extension and the fee for such extension is being paid herewith by electronic transfer. If any additional fee is found due for entry of this amendment, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Liu, reconsider the patentability of all pending claims, in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Liu is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,

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